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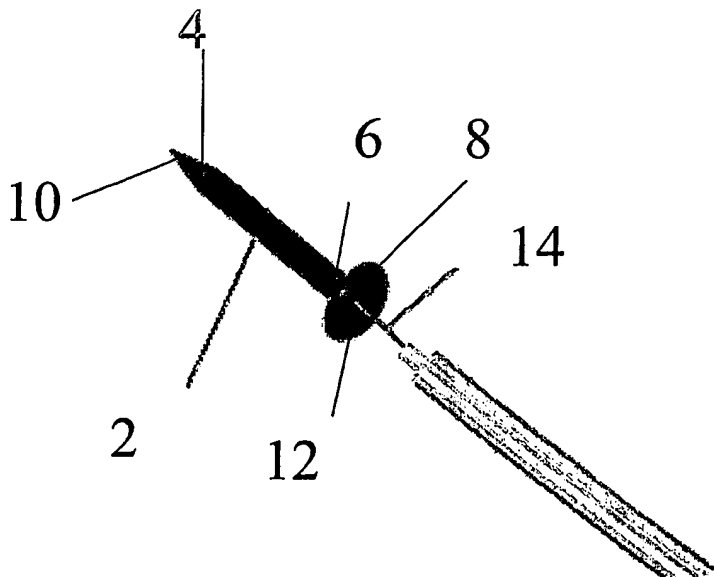
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[Continued on next page]

(54) Title: MEDICAMENT DELIVERY DEVICE AND A METHOD OF MEDICAMENT DELIVERY



(57) Abstract: A medicament delivery device and method of delivering a medicament is provided wherein the device is insertable into the uterine myometrium (in females) and prostate gland (in males) for the delivery of medicaments to the pelvic area and organs thereof, for example the bladder, peritoneum, and in females the vulva, vagina, fallopian tubes, ovaries and uterus and then to the bloodstream.



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1 "Medicament Delivery Device and a Method of
2 Medicament Delivery"

3
4 This invention relates to a medicament delivery
5 device and a method of delivering a medicament. In
6 particular, but not exclusively the present
7 invention relates to a device and a method for
8 providing an implant in the uterine myometrium (in
9 females) or prostate gland (in males) and the
10 delivery of medicament to the pelvic area and organs
11 thereof, for example the bladder, peritoneum, and in
12 females the vulva, vagina, fallopian tubes, ovaries
13 and uterus and then into the bloodstream.

14
15 There are many drugs which may be administered to
16 the human and animal body for the prevention or
17 treatment of disease. Different types of drugs call
18 for different ways of administering the drug to the
19 human or animal body.

20
21 Currently, most benign gynaecological conditions,
22 for example endometriosis or fibroids, are treated
23 using traditional methods of medicament or drug

1 delivery, primarily oral and intravenous
2 administration. Where possible, drugs are provided
3 in pill, capsule, powder or liquid form for oral
4 administration to a human or animal. The drug is
5 then absorbed by the digestive system and will
6 usually enter the blood stream via the liver to take
7 effect. However, far from all drugs are suitable
8 for such administration. For example, many drugs
9 are broken down by the digestion process and
10 destroyed before they can enter the blood stream.
11 This problem is caused by what is commonly referred
12 to as the "first pass liver metabolism" of the human
13 or animal body, i.e. the process by which all
14 substances absorbed by the digestive system must
15 pass through the liver into the blood stream.
16 Therefore, to provide sufficient drug to the female
17 reproductive organs, relatively large doses of a
18 drug are required. These large doses can cause side
19 effects.

20
21 To avoid or minimise the problem of the first pass
22 liver metabolism, drugs can be provided by
23 injection, for example drugs desired to take an
24 instant effect in the blood stream of a human or
25 animal body may be injected into a vein, i.e.
26 intravenously. Alternatively, drugs may be injected
27 into muscle tissue from which the drug is absorbed
28 more slowly into the blood stream. Drugs for
29 injection into muscle tissue may, for example, be
30 provided in an oily base which helps to regulate the
31 rate of absorption. However, injections can be
32 painful and difficult, particularly injections into

1 muscle tissue, and can lead to tissue damage where
2 frequent injections are required on a long term
3 basis, e.g. of insulin for diabetics.

4
5 Other types of drug delivery include nasal sprays
6 for administration of drugs to the nasal tissues and
7 lungs; patches, such as the Nicorette® patch, for
8 the application of Nicotine, or Ortho Evra, a
9 contraceptive patch which releases
10 oestrogen/progesterone through the skin; and lotions
11 or ointments for topical application, i.e. directly
12 to an affected part of the body.

13
14 However, these alternative types of drug delivery
15 means can suffer from disadvantages. For example,
16 skin patches can cause skin irritation, suffer from
17 disattachment and cause cosmetic issues.

18
19 Although the above drug delivery methods are useful
20 for particular types of drugs and medicines, with
21 the exception of intramuscular depot injections,
22 they are unable to provide therapeutic levels of
23 drugs over a long term, e.g. weeks, months and years
24 rather than days, without repeated application by
25 the patient, a carer, physician or general
26 practitioner.

27
28 For application of drugs on a long term basis,
29 various implants have been developed. One such type
30 of implant may be inserted under the skin and have a
31 mechanism for slowly releasing a drug into the blood
32 stream of the human or animal in which it is

1 implanted. For example, Norplant® or Implanon®
2 comprise an implant having small capsules or rods
3 which slowly release levonorgestrel or etonorgestrel
4 into the blood stream to provide a contraceptive
5 effect for women. Norplant® can be effective for up
6 to five years.

7
8 However, these implants inserted under the skin
9 suffer from a number of disadvantages. In
10 particular the insertion of such an implant is
11 painful, can cause significant bruising and
12 discomfort at the implant site and requires local
13 anaesthesia on both insertion and removal. In
14 addition, as such implants are placed under the skin
15 in for example the arm, they can be visible and
16 cause discolouration of the skin. Furthermore, as
17 the arm contains many different types of tissue and
18 planes of tissue, movement of the implant along or
19 through these tissue planes can occur. This can
20 mean the implant moves to locations other than where
21 it was placed during insertion which can lead to
22 complications for the patient, in particular during
23 removal of the implant. Difficulties with the
24 Norplant® implant has led to it being withdrawn from
25 clinical use.

26
27 For gynaecological conditions, long term local drug
28 delivery through the vagina or endometrium is useful
29 to deliver drugs to the pelvic region and organs
30 thereof for example to the bladder, peritoneum,
31 vulva, vagina, ovaries and uterus.

32

1 Current delivery means include vaginal creams, gels,
2 intrauterine devices (contraceptive coils, IUD or
3 IUCD) and vaginal rings or tampons.

4
5 Intrauterine devices (IUDs) are placed in the
6 endometrial cavity typically to provide a
7 contraceptive effect. For example, Leiras (Schering
8 AG) market an intrauterine device called Mirena
9 which releases 20mcg of levonorgestrel, to reduce
10 the thickening of the endometrium of the uterus,
11 each day for up to 5 years.

12
13 Vaginal rings, comprising soft plastic rings of
14 around 4cm to 5cm in diameter impregnated with a
15 desired drug, are placed in the vagina around the
16 cervix where they slowly release a drug into the
17 bloodstream through the soft tissue of the cervix.
18 Organon's Nuvaring releases oestrogen/progesterone.

19
20 Although the above provide long term local drug
21 delivery to the pelvic region, for various reasons,
22 they tend to suffer from low levels of patient
23 compliance.

24
25 Typically creams and gels are considered by patients
26 to be messy and unhygienic while vaginal rings can
27 be uncomfortable, particularly during sexual
28 intercourse, and may cause discharge. Intrauterine
29 devices require inconvenient regular visits to the
30 clinic for physician fitting and can cause severe
31 discomfort such as stomach cramps due to the direct
32 application of levonorgestrel to the endometrium of

1 the uterus. In addition, such intrauterine devices
2 may cause discharge, menstrual disturbance and
3 fertility effects.

4

5 It is an aim of the present invention to provide
6 means to deliver medicaments to the pelvic region
7 which minimises the above difficulties.

8

9 According to the present invention there is provided
10 an implantable medicament delivery device which is
11 insertable into the myometrium or prostate
12 comprising means capable of providing controlled
13 delivery of a medicament over a period of time.

14

15 A medicament may be any pharmaceutical,
16 neutraceutical, prophylactic or therapeutic agent
17 wherein a therapeutic agent includes, but is not
18 limited to, means for radiotherapy such as
19 radioactive sources for example caesium, iridium,
20 radioactive iodine, radioactive strontium or
21 radioactive phosphorus.

22

23 The term "medicament" herein also includes energy
24 sources which may be delivered to the myometrium by
25 targeting the delivery device. Such energy sources
26 include electromagnetic radiation, heating and
27 cooling energies such as to selectively destroy
28 tissues.

29

30 Preferably the medicament delivery device is an
31 implant which can be insertable into the myometrium,

1 or prostate and retainable therein for a defined
2 period of time.

3
4 The retention of the implantable delivery device in
5 the myometrium (in females) or prostate (in males)
6 provides for direct and local delivery of a
7 medicament to the pelvic region and organs thereof
8 for example the bladder, peritoneum, bloodstream and
9 in females the vulva, vagina, ovaries, fallopian
10 tubes and uterus over a determined period of time.

11
12 Preferably the implantable delivery device is
13 capable of being insertable in and retainable in the
14 smooth muscle myometrial tissue of the cervix.

15
16 Insertion and retention of the implantable
17 medicament delivery device in the myometrium of the
18 cervix enables the implant to be checked and
19 monitored by speculum examination or other
20 visualisation or palpation following implantation.

21
22 Alternatively the implantable delivery device may be
23 inserted in any suitable location in the myometrium,
24 usually of the body of the uterus. The implant may
25 be placed in the myometrium of the body of the
26 uterus, or other positions not accessible by access
27 via the vagina.

28
29 Preferably the implantable medicament delivery
30 device comprises a body having an outer surface and
31 opposing first and second ends said body comprising

1 a medicament wherein the first end of the body is a
2 semi-sharp point.

3

4 A semi-sharp point enables the tissue to be
5 sufficiently disrupted to allow insertion of the
6 implantable device, but causes minimal tissue
7 damage.

8

9 In one preferred arrangement the body of the device
10 is elongate and the second end of the body includes
11 a head portion wherein the head portion is a lateral
12 extension from the longitudinal axis of the elongate
13 body.

14

15 Preferably the head portion is a substantially flat
16 plate which extends in all radial directions from
17 the second end of the body of the device.

18

19 The provision of a semi-sharp point at a first end
20 of the delivery device is advantageous as it allows
21 the device to be easily inserted into the smooth
22 muscle of the myometrium or the tissue of the
23 prostate.

24

25 Preferably the means capable of providing the
26 controlled delivery of a medicament over a period of
27 time is a pharmaceutically acceptable carrier such
28 as at least one of a hydrogel, a silicone based
29 material, elastomer, proteinaceous material,
30 polyethylene glycol (PEG) material, polysaccharide
31 or other carbohydrate material, microspheres,
32 polymeric material or plastics material which may

1 comprise, be contained by, or coated onto the
2 device, or other means known to those skilled in the
3 art.

4
5 Preferably the means capable of providing the
6 controlled delivery of a medicament are present in
7 the body of the device.

8
9 Alternatively, in those embodiments wherein there is
10 a head, the means capable of providing the
11 controlled delivery of a medicament may be present
12 in the head of the device.

13
14 In particular embodiments the means are present in
15 both the body and the head of the device.

16
17 In embodiments where the means capable of providing
18 the controlled delivery of a medicament are provided
19 in the body of the device, medicament delivery is
20 substantially through the myometrium to the tissues
21 and organs of the pelvic region.

22
23 In embodiments where the means capable of providing
24 the controlled delivery of a medicament are provided
25 in the head of the device, medicament delivery is
26 substantially to the vaginal cavity and tissues and
27 organs of the pelvic region.

28
29 Preferably the second end of the device includes
30 retrieval means.

31

1 Retrieval means are advantageous as they allow the
2 implant to be removed from the myometrium or
3 prostate tissue after a determined period of time.
4 Thus the delivery device can be easily removed from
5 the body and does not require to be retained in the
6 body forever. Removal of the implantable device
7 provides a means of control over the length of time
8 an active agent of a medicament is delivered.

9
10 The retrieval means can be any means which allow the
11 removal of the implantable device from the
12 myometrium or the prostate following a determined
13 period of time.

14
15 In arrangements of the device which are insertable
16 and retainable in the myometrium, preferably the
17 retrieval means comprises an elongate flexible
18 member, for example a thin length of cord, twine or
19 fibre or string.

20
21 Preferably the elongate flexible member can be left
22 outside the myometrium and soft tissue surrounding
23 the uterus and / or vaginal cavity without causing
24 irritation to a patient, nor affecting sexual
25 intercourse. When it is desired to remove the
26 implantable delivery device from the tissues in
27 which the implant is inserted, for example the
28 myometrium, the flexible member can be manipulated
29 to pull the implant out of the tissue.

30
31 Preferably the second end of the device for example
32 the head and / or retrieval means remain visible or

1 palpable during examination by a physician when, in
2 use, the delivery device is inserted into the
3 myometrium or prostate.

4
5 This is advantageous as the location of the
6 implantable delivery device can be easily monitored
7 and checked by visual or physical inspection.

8
9 Preferably, the overall implantable device of the
10 present invention is significantly smaller than the
11 overall size of coils, IUD or vaginal rings. This
12 is advantageous as there will be less discomfort to
13 the person in which the drug delivery device is
14 implanted and less likelihood of rejection of the
15 implant by the body or responses such as
16 inflammation.

17
18 Preferably the device has an axial length in the
19 range 5 mm to 45 mm.

20
21 More preferably the device has an axial length in
22 the range 10 mm to 45 mm.

23
24 Preferably the device has a diameter of from 0.5 mm
25 to 4 mm.

26
27 Preferably the body has a large surface area to
28 volume ratio. This has the advantage of providing
29 maximal absorption of the drug into the surrounding
30 tissues and / or smooth muscle.

31

1 The device of the present invention may be used to
2 deliver a wide range of active agents for example,
3 but not limited to, steroids, hormones such as a
4 progestin, agents which promote a contraceptive
5 effect, for example levonorgestrel or etonorgestrel,
6 agents for treating disorders of the pelvis, for
7 example, GnRH analogues, NSAIDs, COX-II inhibitors
8 and aromatase inhibitors, vagina and organs and
9 tissues thereof, cytotoxic agents for killing cancer
10 cells or treating cancer, particularly cancer cells
11 of the bladder, prostate or cervix or other pelvic
12 malignancies and agents for the treatment of benign
13 prostatic hypertrophy, impotence, erectile
14 dysfunction and the like. Further, the device may
15 be used to deliver agents for the treatment of an
16 over active bladder, such drugs including anti-
17 cholinergic drugs or calcium antagonists, or agents
18 for radiotherapy.

19

20 Preferably the medicament of the device is chosen
21 from the group consisting of, but not limited to,
22 anti-infectives, antimicrobials, antivirals,
23 antibiotics, anti-allergens, anti-inflammatories,
24 anti-fungals, anti-cholinesterases, nutritional
25 agents such as essential amino-acids, fats and
26 vitamins, prebiotics, probiotics and acidifiers,
27 cardiovascular agents, anti-hypertensive agents and
28 chemotherapeutic agents.

29

30 Preferably the medicament is a therapy for oestrogen
31 dependent proliferative disorders of the pelvis, for
32 example endometriosis and / or fibroids and other

1 pelvic disorders as would be known to those skilled
2 in the art for example functional cysts and
3 polycystic ovary syndrome.

4
5 Preferably said therapy for endometriosis includes
6 progestins, GnRH agonists and antagonists, NSAIDs,
7 COX-II inhibitors, combined oral contraceptives,
8 Danazol, smooth muscle relaxants or aromatase
9 inhibitors. The skilled person would also appreciate
10 other similar therapies which could be used in
11 relation to such disorders and the suitable dosage
12 that would be required.

13
14 A drug delivered by the present invention may
15 additionally or alternatively include a microbicide.
16 A microbicide is any agent detrimental to, or
17 destructive of, the life of microbes, viruses or
18 bacterial organisms. Such a microbicide could be
19 used to destroy organisms responsible for sexually
20 transmitted diseases such as gonorrhoea, chlamydia,
21 genital herpes, Human Immunodeficiency Virus, Human
22 Papilloma Virus or bacterial vaginosis.

23
24 The concentration and the time period over which the
25 above active agents and those described below should
26 be provided will be as determined by those skilled
27 in the art. Those skilled in the art can determine
28 these parameters, which depend on for example the
29 potency (the amount required to effect the desired
30 change), toxicity and in vivo diffusion of the
31 active agent using standard procedures.

32

1 Preferably, in use, the cumulative release of
2 therapeutic agent is in an amount selected from 5%,
3 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%,
4 90%, 95%, 99% and 100% relative to the total amount
5 of medicament in the device after implantation for a
6 period of 1 week, 2 weeks, 1 month, 2 months, 3
7 months, 4 months, 6 months, 1 year, 2 years, 3
8 years, 4 years or 5 years.

9
10 According to a second aspect of the present
11 invention there is provided a kit for implanting a
12 device of the first aspect of the invention
13 comprising
14 a device according to the first aspect of the
15 invention and an insertion tool, said tool
16 comprising an elongate shaft, said shaft having
17 handle means at a first end thereof and device
18 mounting means at a second opposite end wherein
19 the medicament delivery device of the first
20 aspect of the invention is mountable on the
21 insertion tool.

22
23 According to a third aspect of the present invention
24 there is provided a method of providing a medicament
25 to a female mammal comprising the step of inserting
26 a device according to a first aspect of the
27 invention into the myometrium.

28
29 The implantable delivery device is capable of being
30 inserted into the smooth muscle myometrial tissue of
31 the cervix via the vagina, into the myometrium of
32 the uterine body through serosa surrounding the

1 myometrium during open or laparoscopic surgery or
2 into the myometrium through the endometrial cavity.

3

4 Preferably the method of the third aspect of the
5 invention comprises the steps of

6 a) providing the implantable medicament
7 delivery device of the first aspect of the
8 invention,

9 b) introducing the medicament delivery device
10 into the body via the vagina,

11 c) penetrating the myometrium with the
12 medicament delivery device, and

13 d) inserting the medicament delivery device
14 into the myometrium.

15

16 Preferably the method further comprises the step of
17 mounting the implantable medicament delivery device
18 on an insertion tool.

19

20 Particular embodiments of the medicament delivery
21 device are implantable in the prostate. The
22 prostate is a gland in males which surrounds the
23 urethra below the bladder.

24

25 Preferably the implant is insertable into the
26 prostate by a transrectal route. Alternatively the
27 implant can be inserted into the prostate by a
28 trans-perineal route.

29

30 Preferably the medicament delivery device is
31 insertable into the prostate using ultrasound.

32

1 Provision of an implantable medicament delivery
2 device in the prostate has the advantage that drugs
3 can be delivered to the tissue of the prostate,
4 tissue surrounding the prostate, and the
5 bloodstream. Further, delivery of drugs directly to
6 the prostate means the drugs are not subjected to
7 liver metabolism as would be the case for drugs
8 provided orally.

9
10 Preferably the prostate implantable medicament
11 delivery device provides for the cumulative release
12 of a therapeutic agent in an amount selected from
13 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%,
14 80%, 90%, 95%, 99% and 100% relative to the total
15 amount of medicament in the device after
16 implantation for a period of 1 week, 2 weeks, 1
17 month, 2 months, 3 months, 4 months, 6 months, 1
18 year, 2 years, 3 years, 4 years or 5 years.

19
20 According to a fourth aspect of the present
21 invention there is provided the use of a delivery
22 device according to the first aspect of the
23 invention to provide long term local delivery, for
24 example 3 months to 5 years, of medicaments to the
25 pelvic region and organs thereof, for example to the
26 bladder, peritoneum, vulva, vagina, ovaries and
27 uterus.

28
29 In one preferred embodiment of the fourth aspect of
30 the invention a device according to the first aspect
31 of the present invention is used to deliver
32 medicament(s) to treat gynaecological conditions,

1 for example endometriosis, fibroids, cervical cancer
2 or overactive bladder.

3
4 In a second preferred embodiment of the fourth
5 aspect of the invention a device according to the
6 first aspect of the present invention is used to
7 treat male conditions for example benign prostatic
8 hypertrophy, impotence, erectile dysfunction and the
9 like.

10
11 The medicament delivery device and method of the
12 present invention promote smooth, controlled release
13 of drugs to the pelvic region, which allows
14 absorption of drugs without subjecting drugs to
15 liver metabolism.

16
17 Embodiments of the present invention will now be
18 described by way of example only with reference to
19 the accompanying drawings, in which:

20
21 Figure 1 is an illustration of an implantable
22 medicament delivery device according to the
23 invention for delivery of medicament to the
24 tissues of the myometrium and pelvic region;

25
26 Figure 2 is an illustration of an implantable
27 medicament delivery device according to the
28 invention for delivery of medicament to the
29 tissues of the vaginal cavity and pelvic
30 region;

31

1 Figures 3, 4, 5 and 6 are illustrations of
2 embodiments of the medicament delivery device
3 according to the invention;

4
5 Figure 7 is a sagittal illustration of the
6 female pelvic region of a medicament delivery
7 device of Figure 1 in use;

8
9 Figure 8 is an end view of the illustration in
10 Figure 4 along the line A-A illustrating the
11 placement of the device;

12
13 Figure 9 is a coronal view of the illustration
14 in Figure 4 along line B-B;

15
16 Figure 10 shows an illustration of the
17 embodiment of a medicament delivery device as
18 shown in figure 1 mounted on an insertion tool;

19
20 Figure 11 shows an illustration of the
21 embodiment of a medicament delivery device as
22 shown in figure 2 mounted on an insertion tool;

23
24 Figure 12 shows an illustration of an
25 embodiment of device mounting means wherein the
26 mounting means are formed by a stepped
27 protrusion on the insertion tool capable of
28 cooperating with a depression provided on the
29 delivery device;

30
31 Figure 13 shows an embodiment of a handle means
32 of an insertion tool; and

1

2 Figure 14 is an illustration of an embodiment
3 of an implant of the present invention inserted
4 in the prostate.

5

6 Referring to Figure 1, in one embodiment, the
7 implantable medicament delivery device comprises an
8 elongate cylindrical body 2 with a first end 4 and a
9 second end 6. In this embodiment head portion 8
10 extends laterally from the second end 6 of the body
11 2 such that a flange is provided around the
12 circumference of the body 2 at the second end. A
13 semi-sharp point 10 is provided at the first end 4
14 of the body 2. In the embodiment shown the head
15 portion 8 is a substantially flat plate which
16 includes a depression 12. When, in use, the body of
17 the device is implanted in the tissues of the
18 myometrium, the head portion 8 minimises the
19 likelihood of the tissue of the implant being pushed
20 too far into the tissue during insertion of the
21 implant or the myometrium tissue growing over the
22 implant. It also provides means by which the
23 position of the implant can be checked by visual or
24 physical means.

25

26 In the embodiment described which is insertable into
27 the myometrium, retrieval means 14 are provided by a
28 cord. The cord extends substantially from the
29 centre point of the depression 12 in the head
30 portion 8. In use, the cord extends from the second
31 end of the implant and allows the device to be
32 removed from the tissue after suitable delivery of

1 the medicament or if the patient requests removal.
2 The device is typically retained in the body for at
3 least a day, a few weeks, months or up to 5 years.
4 It may be removed at any point during this period.
5 In embodiments wherein the device is comprised of
6 biodegradable material the device may not need to be
7 removed at a later time point and thus will not
8 require a head portion or retrieval means.

9
10 In this embodiment the means capable of providing
11 controlled delivery of the medicament is located in
12 or on the elongate body 2 of the device. Delivery
13 of the medicament is substantially through the
14 myometrium and into pelvic organs and tissues. This
15 embodiment of the device is particularly
16 advantageous for the delivery of medicament for the
17 treatment of endometriosis and or fibroids.

18
19 Figure 2 shows an embodiment of the present in
20 invention wherein the elongate body 2 may be shorter
21 in length, approximately 5 mm to 20 mm in length and
22 in which the head portion 8 is larger typically
23 around 12 mm in width. In such an embodiment the
24 means capable of providing controlled delivery of a
25 medicament over a period of time is located in or on
26 the head portion.

27
28 In use, the body 2 is inserted in the tissues of the
29 myometrium and the head portion remains in the
30 vaginal cavity. This embodiment of the device
31 substantially delivers medicament to the vaginal
32 cavity, mucosa thereof and pelvic tissues, such an

1 embodiment is particularly advantageous for delivery
2 of medicaments suitable for treating bacterial
3 vaginosis.

4
5 Alternative embodiments of the implantable device
6 are illustrated by figures 3 to 6. In these
7 embodiments the body of the implant may be spiral or
8 corkscrew shaped (figure 3), generally J or U shaped
9 such that the second end of the implant forms a loop
10 or hook (figures 4 and 6) or an elongate mesh
11 cylinder (figure 5). As shown in figure 4 a semi-
12 sharp point may not be required at the first end of
13 the body 4 to allow insertion into the tissues.

14
15 The body may be any suitable shape which allows the
16 implant to be inserted into the myometrium or
17 prostate. Indeed the cross section of the body can
18 be of any preferred shape, which allows insertion of
19 the implant into the myometrium or prostate, or that
20 influences the drug delivery characteristics of the
21 implantable delivery device. For example the body
22 of the device may be cross-shaped to increase the
23 surface area of the delivery device exposed to the
24 surrounding tissue. Further, the body may be formed
25 by a mesh or other method to increase the surface
26 area of the implant in contact with the myometrial
27 or prostate tissue. The amount of surface area of
28 the implant in contact with surrounding tissue or
29 muscle can influence the drug delivery
30 characteristics of the implant.

31

1 As shown in figures 4 and 6 the retrieval means may
2 comprise a hook at the second end of the implantable
3 device wherein the second end of the body 2 is bent
4 toward the first end to provide a hook. In this
5 embodiment the retrieval means restricts the body 2
6 from becoming buried in the soft tissue enabling
7 retrieval of the implant from soft tissue and the
8 smooth muscle of the myometrium or the prostate. In
9 addition, the hook provides means by which the
10 location of the implant can be checked by a
11 physician by visual or physical means.

12
13 Alternatively, as shown in figure 3, the retrieval
14 means can be a slot capable of accepting a
15 screwdriver or other means for rotating the
16 implantable delivery device in the tissue to insert
17 or remove the device from the tissue.

18
19 In the embodiment illustrated by figure 1 the body 2
20 comprises the medicament delivery means. In
21 particular embodiments, not shown in figure 1, a
22 length of the body 2 between the point 4 and
23 retrieval means 14 may have a reduced diameter
24 relative to the diameter of the body 2 at the first
25 4 and second ends 6. In such embodiments the drug
26 delivery means may comprise a cylinder of material
27 formed around the reduced diameter portion of the
28 body 2. The medicament delivery means can be any
29 suitable pharmaceutically acceptable carrier for
30 example, a hydrogel carrying the active agent to be
31 delivered by the medicament delivery device. In
32 another example, the delivery means is a silicone

1 based material, elastomer, proteinaceous material,
2 polyethylene glycol (PEG) material, polysaccharide
3 or carbohydrate material, microspheres, polymeric
4 material or plastics material which may comprise, be
5 contained by, or coated onto the device. The above
6 drug delivery devices may also comprise, be
7 contained by, or coat the head 8 of the device.
8 This allows, as discussed in relation to the
9 embodiment illustrated in figure 2, for delivery of
10 medicament to the vaginal cavity.

11

12 In a preferred embodiment, the body of the implant
13 which may be porous, non-porous or microporous, can
14 be dipped into a solution of the selected drug
15 delivery medium containing a solution or slurry of
16 drug, such that a thin layer of drug and drug
17 delivery medium is coated onto the body of the
18 implant and bonds securely in the dry state to the
19 body of the implant via a mechanical or adhesive
20 hold.

21

22 Alternatively, the medicament can be impregnated, or
23 absorbed by or into the device and allow the
24 medicament to be released over time. As a further
25 alternative the medicament may be applied to the
26 device using any suitable means that allow the
27 medicament to be attached or bonded to the device
28 and which allow the medicament to be available for
29 absorption / release into the surrounding tissues,
30 for example the myometrium or vaginal cavity.

31

1 The drug delivery medium may be capable of slowly
2 releasing the active agent of the medicament into
3 the myometrium, vaginal cavity or the prostate, and
4 thus providing drugs to the pelvic region and organs
5 thereof the surrounding soft tissues and blood
6 vessels.

7
8 Hydrogel releases drug by diffusion or via
9 microcracks in the hydrogel. An alternative
10 biodegradable hydrogel system releases drug via an
11 erosion or degradation mechanism. Varying release
12 rates of drugs can be achieved, as can continuous
13 dosing with small levels of drugs, and flexibility
14 of drug release may depend on different drugs being
15 utilised

16
17 Depending of the release characteristics of the
18 hydrogel and the chemical composition of the active
19 agent; release of the active agent will typically
20 occur up to 5 years from implantation of the
21 delivery device.

22
23 The medicament delivery device may be formed by any
24 biocompatible material, for example the medicament
25 delivery device can be formed from plastics or
26 biocompatible metals. Suitable materials include,
27 but are not limited to, high density polyethylene
28 (HDPE), ultra high molecular weight polyethylene
29 (UHMWPE), polypropylene (PP), polyvinyl chloride
30 (PVC), polymethylmethacrylate (PMMA),
31 polyethyleneterephthalate (PET), polytetra-
32 fluoroethylene (PTFE), polycarbonate (PC), styrene-

1 butadine-styrene (SBS), stainless steel
2 (361/316L/317), nickel free stainless steel, cobalt
3 chrome alloy (CoCrMo), titanium (specifically
4 Ti6Al4V) and Liquid Metal.

5
6 In one particular embodiment of the delivery device,
7 the delivery device is formed from the medium
8 carrying the drug. In this example, if the medium
9 carrying the drug is absorbable, the complete
10 delivery device may be absorbed by the body over the
11 period of time that the drug is administered.

12
13 Wherein the implant itself is the medium by which
14 the drug to be administered is carried it can be
15 envisaged that an insertion device for example a
16 trocar containing the implant may be used to deliver
17 the implant. In this embodiment the delivery device
18 may be pushed out of or injected from the trocar
19 into the myometrium 44. The use of an implant
20 comprising the medium in which the drug to be
21 administered is included, would allow insertion of
22 the implant into the myometrium 44 and delivery of
23 the drug to be limited to a shorter time scale for
24 example 1 day, 3 months to 12 months. The implant
25 would not require to be removed at a later date as
26 it may degrade over time and be absorbed by the
27 body.

28
29 The drug may be delivered to the myometrium 44 and
30 be absorbed within a few minutes, hours, days or
31 weeks depending on the medium. It can be
32 appreciated that where the implant comprises the

1 drug delivery medium, removal of the implant is not
2 required. An absorbable implant therefore does not
3 require retrieval means.

4
5 The uterine myometrium has few or no somatic pain
6 fibres and thus insertion, provision and withdrawal
7 of the implant in the myometrium will cause minimal
8 pain and discomfort to the patient.

9
10 A device of the present invention capable of being
11 implanted into the myometrium tissue is advantageous
12 over subcutaneous delivery devices previously known
13 in the art, such as Norplant® which are inserted
14 under the skin which has somatic sensory (pain)
15 nerves.

16
17 As there is little tissue or muscle movement in the
18 myometrium compared with for example the tissues of
19 the arm or the leg and the myometrium does not
20 comprise as many layers or planes of tissue as in
21 the arm or leg, there is little likelihood of the
22 implant moving to a different location following
23 insertion.

24
25 As shown in Figure 7, the female human genital area
26 comprises a bladder 30, urethra 32, vaginal cavity
27 34, cervix 36, uterus 38 and anus 40. In
28 particular, the cervix 36, at a position between the
29 vaginal cavity 34 and uterus 38, comprises the
30 cervical canal 42 leading from the vaginal cavity 34
31 into the uterus 38 and surrounding smooth muscle
32 known as the myometrium 44. The myometrium is

1 defined by the serosa 46 (an epithelial layer of
2 cells) and the endometrium 48. An end view of the
3 cervix along line A-A is shown in Figure 8.

4

5 In use, an embodiment of the implant can be inserted
6 into the myometrium via the vagina and then through
7 the cervix or alternatively may be inserted into the
8 myometrium during open or laproscopic surgery.

9

10 The myometrium of the cervix is in a convenient
11 location, at the top of the vaginal cavity, for
12 insertion and removal of the implant via vaginal
13 access. Further insertion of the device by this
14 route has the advantage that the implant can be
15 suitably located using a speculum in an outpatient
16 setting. The insertion of the implant in the
17 myometrium would be similar in both the time taken
18 and the discomfort to the patient as the taking of a
19 smear.

20

21 Insertion of the implantable medicament delivery
22 device during open or laproscopic surgery has the
23 advantage of allowing the implant to be placed at
24 any suitable location in the myometrium, usually in
25 the body of the uterus. The implant may thus be
26 placed in the myometrium of the body of the uterus,
27 or other positions which would not be accessible by
28 access via the vagina.

29

30 Location of the implant within the smooth muscle
31 myometrial tissue of the cervix and uterus provides
32 a novel means of drug delivery to the pelvic region

1 and organs thereof for example to the bladder,
2 peritoneum, vulva, vagina, ovaries and uterus.
3 Local delivery of active agents of a medicament via
4 insertion of the implant in the uterine myometrium
5 promotes rapid, efficient absorption of the active
6 agent directly into these organs the surrounding
7 tissue and then the bloodstream. Further, delivery
8 of medicaments in this way avoids the first pass
9 liver effect.

10

11 The active insertion of the implantable delivery
12 device into the smooth muscle of the cervix of the
13 uterine body means that the present invention
14 differs from an IUD or a vaginal ring as an IUD is
15 located in the cavity of the uterus (endometrium)
16 and vaginal rings are placed at the top of the
17 vagina around the cervix.

18

19 While inserted in the myometrium the device will not
20 be felt by the patient. As previously discussed,
21 this provides a further advantage of the present
22 invention over intrauterine devices and vaginal
23 rings. Furthermore, the device of the present
24 invention will not cause menstrual or fertility
25 disturbances and will be acceptable to women of a
26 range of religious faiths.

27

28 Moreover, drug delivery by means placed around
29 tissues or in cavities such as vaginal rings and
30 intrauterine devices can suffer from decreased
31 absorption as the active agents have to pass through
32 epithelial layers overlying the surrounding tissues

1 before they enter the tissue. For example, drugs
2 released from a vaginal ring must pass through the
3 vaginal epithelium before being absorbed into the
4 vaginal wall and passing into the blood stream.

5
6 Locating medicament delivery means and delivery of
7 the medicament in the myometrium minimises the risk
8 of poor absorption as the active agents are not
9 required to pass through epithelium. Medicament
10 absorption is facilitated by high local blood flow.

11
12 In particular embodiments locating medicament
13 delivery means in the myometrium and delivery of the
14 medicament into the vaginal cavity enables delivery
15 to the epithelium lining the vagina and the local
16 tissues thereof.

17
18 Therefore drug delivery directly into the myometrium
19 or vagina will likely require smaller amounts of a
20 drug to achieve significant clinical affect,
21 substantially reducing the risk of side effects.

22
23 In specific embodiments of the medicament delivery
24 devices, suitable for delivery of drugs to the
25 tissues of the myometrium, for example figure 1, the
26 body 2 of the medicament delivery device typically
27 has a diameter of 2 mm and a length of 20 mm. These
28 diameters and lengths are, of course, for guidance
29 only and other suitable dimensions will be apparent
30 to those skilled in the art. For example depending
31 of the amount of drug to be delivered the length of
32 the body may be 20mm or 30mm.

1
2 Figure 2 shows an embodiment of the device for
3 delivery of drugs to the vaginal cavity. In this
4 embodiment, the body is preferably around 5 to 10 mm
5 in length and the head is around 8 to 15 mm in
6 width.

7
8 The implant may have any structure suitable for
9 insertion and retention in the smooth muscle of the
10 myometrium or the tissue of the prostate. For
11 example the implant may comprise barbed portions or
12 surface patterns to promote retention of the implant
13 in the myometrium or prostate. This may be
14 advantageous if movement of the tissue in which the
15 implant is inserted is likely to cause the implant
16 to work loose and move from its intended position.

17
18 To aid insertion of the medicament delivery device
19 into the myometrium by a vaginal route an insertion
20 tool may be used.

21
22 An embodiment of an insertion tool is shown in
23 figures 10 and 11 with the implantable devices
24 illustrated by figure 1 and 2 respectively mounted
25 thereon. In the embodiment shown, the insertion tool
26 comprises a curved stainless steel shaft 60 of
27 approximately 20 to 25 cm in length and around 2 mm
28 in diameter. A handle element 62 of around 2 to 4
29 cm may be provided on the shaft. A particular
30 embodiment of a handle element is illustrated in
31 figure 13.

32

1 A first end of the shaft is provided with device
2 mounting means 74 and a second end is provided with
3 handle means 62. In the example shown the device
4 mounting means, illustrated more clearly in figure
5 12, comprises a stepped protrusion 66 which provides
6 a surface 68 against which the second end of the
7 implantable device can abut. In particular, as
8 shown in figure 12 a protruding portion 70 of the
9 device mounting means is received by the depression
10 12 provided on the head portion 8 of the implantable
11 device. The cord 14 of the implantable device is
12 pulled along the length of the shaft 60 and is
13 releasably fixable in a notch 72 provided in the
14 handle means 62 of the insertion tool. The fixing
15 of the cord 14 in the notch 72 aids the mounting of
16 the device on the shaft of the insertion tool.

17

18 The device is mounted on the first end of the
19 insertion tool and then the device is introduced
20 into the body via the vagina. Using the insertion
21 tool the device is advanced into the vagina 34
22 towards the cervix 36 and inserted into the
23 myometrium 44. The point 4 of the implant
24 facilitates the easy insertion into the smooth
25 muscle of the myometrium 44.

26

27 The device is inserted into the myometrium until
28 only the head portion of the device or retrieval
29 means remain outside.

30

31 After a determined period of time, the implant can
32 be removed from the myometrium. Removal may be due

1 to the implant reaching the end of its useful life,
2 i.e. the drug has been administered for the intended
3 length of time or the patient requesting removal of
4 the implant. The implantable delivery device can be
5 removed by pulling on the retrieval means 14, for
6 example a cord or hook to withdraw the implant from
7 the myometrium 44. Again, this is a straightforward
8 procedure without routine need for local
9 anaesthetic.

10

11 The delivery device is typically removed from the
12 tissue after it has released a therapeutic agent in
13 an amount selected from 5%, 10%, 15%, 20%, 25%, 30%,
14 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% and 100%
15 relative to the total amount of medicament in the
16 device after implantation for a period of 1 week, 2
17 weeks, 1 month, 2 months, 3 months, 4 months, 6
18 months, 1 year, 2 years, 3 years, 4 years or 5
19 years.

20

21 Alternative insertion tools may be used to insert
22 the device.

23

24 For example if the implant has a blunt first end 4,
25 as illustrated in figure 4, an insertion tool with a
26 semi-sharp point may be used to penetrate the
27 myometrium or prostate tissue and enable insertion
28 of the implant.

29

30 This may be advantageous, as the implant which is
31 retained in the tissue does not then require to have
32 a semi-sharp portion.

1
2 In further embodiments of the insertion tool,
3 instead of or in addition to device mounting means,
4 the insertion tool may comprise means for releasably
5 containing the implant within the tool. This
6 embodiment of the insertion tool is driven into the
7 myometrium, the implantable device is released into
8 the myometrium and the tool is then withdrawn
9 leaving the implant in place. For example, the
10 insertion tool may comprise a collar for releasably
11 retaining the medicament delivery device.

12
13 During insertion, use and removal the implantable
14 device may be manipulated using any suitable
15 surgical tool, such as forceps or the like.

16
17 As discussed above, the implantable medicament
18 delivery device can be provided with medicament for
19 release into the surrounding tissues in a number of
20 ways.

21
22 Where the medium carrying the active agent of the
23 medicament is provided by the body of the delivery
24 device, the agent is released from the medium and
25 passes through drug delivery means present in the
26 delivery device to enter the surrounding tissue, for
27 example the myometrial tissues. Drug delivery means
28 may be provided along the entire length, at least
29 part of the body, the head, or the body and head of
30 the implantable device.

31

1 When inserted in the myometrium the body of the
2 medicament delivery device is surrounded by smooth
3 muscle and soft tissue. As smooth muscle of the
4 cervix is highly vascularised, drug delivery to
5 these tissues show good pharmacokinetics.

6
7 These drugs are able to pass through the highly
8 vascularised tissues of the myometrium and target
9 the pelvic region and organs thereof, for example,
10 the bladder, peritoneum, and in females the vulva,
11 vagina, ovaries and uterus. The drugs may further
12 enter the bloodstream without being subjected to
13 first pass liver metabolism.

14
15 Alternatively, drug delivery means may be provided
16 at the head portion at the second end of the
17 delivery device. When, in use, the implant is
18 inserted into myometrial tissue, the head portion
19 protrudes from the myometrial tissue into the
20 vagina. In this particular embodiment, the implant
21 provides a means of targeting drug delivery to the
22 tissues of the vagina.

23
24 The implantable delivery device may be retained in
25 the myometrium or the prostate and drug delivered
26 over a period of at least, 1 day, 1 to 3 months, 1
27 to 6 months, 1 to 12 months, 1 to 2 years, 1 to 3
28 years or 1 to 5 years.

29
30 The implant of the present invention may be used to
31 deliver a wide range of drugs. In particular, the

1 implant can be used to deliver drugs which cannot be
2 delivered orally.

3

4 Examples of conditions which can be treated using
5 the drug delivery device will now be provided.

6

7 **Endometriosis**

8

9 Endometriosis is a painful condition caused by the
10 endometrium (cells lining the uterus) migrating to
11 other parts of the body. This can cause functional
12 and hormonally responsive endometrial lesions.
13 Typically lesions are found on the uterine muscles,
14 ovary, peritoneum and intestine. Symptoms of
15 endometriosis include excessive bleeding,
16 dysmenorrhoea, pelvic pain and infertility (up to
17 60% of women suffering from endometriosis become
18 infertile).

19

20 **Fibroids**

21

22 Fibroids or myoma are benign encapsulated tumours of
23 the smooth muscle and / or fibrous tissue elements
24 of the uterine myometrium. They are usually
25 asymptomatic, but may give rise to menstrual and /
26 or fertility problems.

27

28 At present, an oral treatment (Danazol) is one of
29 the most effective drugs to treat endometriosis, but
30 the androgenic side effects of this drug limits
31 treatment to 6 months. Endometriosis can also be
32 treated using subcutaneous depot injections or nasal

1 sprays of GnRH analogues. However, these treatments
2 also have unpleasant side effects such as bone
3 density loss, hot flushes and nausea.

4
5 The present implantable medicament delivery device
6 provides pharmacokinetic advantages over the above
7 for the treatment of endometriosis and fibroids. In
8 particular the present delivery system provides long
9 term delivery of a drug locally to the pelvic
10 region, without the disadvantage of current local
11 delivery systems such as vaginal rings or
12 intrauterine devices.

13
14 A number of active agents may be provided using the
15 device of the present invention for treatment of
16 endometriosis.

17
18 **Progestin**

19
20 Progestins have advantages over Gonadotrophin
21 Releasing Hormone (GnRH) Agonists in that they are
22 cheaper with an improved side effect profile. In
23 addition, Progestin therapy is most effective in
24 controlling the symptoms associated with
25 endometriosis, more specifically dysmenorrhea.

26
27 Progestin refers to synthetic progestogens wherein
28 Progestogen is a generic term for all substances
29 with progesterone like activity. Progesterone refers
30 to the natural progesterone molecule.

31

1 There are two main groups of progestogen,
2 progesterone and its analogues (dydrogesterone,
3 gestrinone and medroxyprogesterone) and testosterone
4 analogues (norethisterone and norgestrel). The newer
5 progestogens (desogestrel, megestrol,
6 norelgestromin, norgestimate, etonogestrol,
7 ethynodiol or ethynodiol and gestodene) are all
8 derivatives of norgestrel; levonorgestrel is the
9 active isomer of norgestrel and has twice its
10 potency. Progesterone and its analogues are less
11 androgenic than the testosterone derivatives.
12 Testosterone analogues are the norethindrone family
13 (estranes) - including norethindrone, norethindrone
14 acetate, ethynodiol diacetate, lynestrenol, and
15 norethisterone acetate; and the levonorgestrel
16 family (gonanes) - including levonorgestrel,
17 norgestrel, desogestrel, norgestimate, gestodene,
18 megestrol, norelgestromin, and etonogestrol.

19

20 Common progestins include medroxyprogesterone and
21 levonorgestrel.

22

23 Non Steroidal Anti Inflammatory Drugs (NSAIDs)

24

25 Non Steroidal Anti Inflammatory Drug (NSAIDs)
26 have good efficacy, low cost and comparatively mild
27 side effect profile, and offer immediate pain
28 management. They are most effective in controlling
29 the symptoms associated with endometriosis. Common
30 NSAID's include mefenamic acid, diclofenac or
31 piroxicam.

32

1 **GnRH Analogues**

2

3 The main therapy shown to improve the severity of
4 endometriosis is the gonadotrophin releasing hormone
5 (GnRH) agonists.

6

7 However, this class suffers two main drawbacks,
8 these being cost and severe side effects profile
9 primarily bone density loss associated with inducing
10 a temporary chemical menopause. Common GnRH
11 agonists include leuprolide, goserelin and
12 nafarelin.

13

14 In addition to the above sole therapies the device
15 of the present invention can also be used to deliver
16 a number of combination therapies. For example,
17 Progestin/NSAID,
18 Progestin/GnRH analogues,
19 GnRH/NSAID or,
20 GnRH add back therapy (tibolone)

21

22 **GnRH with add back therapy**

23

24 Add-back therapy in conjunction with a GnRH agonist
25 does not eradicate bone loss, however it does reduce
26 the rate of bone demineralization and hence, enable
27 longer use of GnRH agonists. The progestin tibolone
28 is of particular interest for use as add back
29 therapy, particularly for osteoporosis prophylaxis.

30

31 Owing to the poor solubility of all proposed drugs
32 in water, a hydrogel (flooded with water, thus low

1 driving force only required to release drugs) is
2 ideally used as the drug carrier on the implant. The
3 porous but permeable active drug/carrier can be
4 coated onto the body of the implant via
5 mechanical/adhesive hold. In such an embodiment a
6 microporous implant may be necessary. This exterior
7 coating of hydrogel/active drug may be biodegradable
8 and should be a highly concentrated but thin layer
9 (high drug reservoir/ low distance to travel) to
10 obtain maximum rate of drug release via an erosion
11 mechanism.

12
13 The amount of drug required to elicit effect can be
14 determined by those skilled in the art, using
15 conventional means. However, estimates of the
16 amount of a drug which may be provided based on
17 preliminary results which should not be considered
18 limiting in any way on the device of the present
19 invention are given below by way of example only.

20
21 **Levonorgestrel**

22
23 Currently, oral daily doses for levonorgestrel are
24 60mcg. Using vaginal delivery analogy of 10% drug
25 required compared to oral doses, daily myometrial
26 doses would be 6mcg for levonorgestrel

27
28 A more feasible daily dose to enable drug delivery
29 via a hydrogel would likely be 20mcg for
30 levonorgestrel (33% of oral dose)

31

1 Assuming 50% w/w of drug to hydrogel, the total
2 weight of the drug/carrier layer could be in the
3 range of 3 to 15 mg.

4
5 The body of the implant could accommodate 3, 6 or 12
6 month or longer doses.

7

8 Leuprolide

9

10 Currently, the daily dose for leuprolide is 125mcg
11 (intramuscular). Typical daily myometrial doses
12 could be around 62 mcg for leuprolide (50% of
13 intramuscular dose)

14

15 However in the absence of clinical data, it is
16 impossible to estimate the clinical effectiveness of
17 such doses of leuprolide.

18

19 Assuming 50% w/w of drug to hydrogel, the total
20 weight of the drug/carrier layer would be in the
21 range of 10m to 45 mg.

22

23 The body of the implant could accommodate 3, 6 or 12
24 month or longer doses.

25

26 Piroxicam

27

28 Currently, oral daily doses for piroxicam are 10 to
29 40mg. Using vaginal delivery analogy of 10% drug
30 required compared to oral doses, a daily myometrial
31 doses could be 3mg for piroxicam. A more feasible
32 daily dose to enable drug delivery via a hydrogel

1 could be 300mcg for piroxicam (1% of oral dose).
2 However in the absence of clinical data, it is
3 impossible to estimate the clinical effectiveness of
4 such low doses of piroxicam.

5
6 Assuming 50% w/w of drug to hydrogel, the total
7 weight of the drug/carrier layer would be around 50
8 to 220 mg.

9
10 The body of the implant could accommodate 3, 6, or
11 12 month or longer doses.

12

13 **Levonorgestrel/Piroxicam**

14

15 Currently, oral daily doses for levonorgestrel are
16 60mcg, and piroxicam 10-40mg. Using vaginal delivery
17 analogy of 10% drug required compared to oral doses,
18 daily myometrial doses could be 3mg for piroxicam
19 6mcg for levonorgestrel. A more feasible daily dose
20 to enable drug delivery via a hydrogel
21 (levonorgestrel dose as per Mirena coil dose) would
22 be 300mcg for piroxicam (1% of oral dose), 20mcg for
23 levonorgestrel (33% of oral dose). However in the
24 absence of clinical data, it is impossible to
25 estimate the clinical effectiveness of such low
26 doses of piroxicam.

27

28 Assuming 50% w/w of drug to hydrogel, the total
29 weight of the drug/carrier layer would be in the
30 range of around 55 mg to 230 mg.

31

1 The body of the implant could accommodate 3, 6, 12
2 month or longer doses.

3

4 **Levonorgestrel/Leuprolide**

5

6 Currently, daily doses for levonorgestrel are 60mcg
7 (oral), and leuprolide 125mcg (intramuscular). Using
8 vaginal delivery analogy of 10% drug required
9 compared to oral doses, daily myometrial doses could
10 be 62.5 mcg for leuprolide and 6 mcg for
11 levonorgestrel. A more feasible daily dose to
12 enable drug delivery via a hydrogel would be 62.5mcg
13 for leuprolide (50% of intramuscular dose) and 20mcg
14 for levonorgestrel (33% of oral dose). However in
15 the absence of clinical data, it is impossible to
16 estimate the clinical effectiveness of such low
17 doses of leuprolide.

18

19 Assuming 50% w/w of drug to hydrogel, the total
20 weight of the drug/carrier layer could be in the
21 range of around 14 mg to 60 mg.

22

23 The body of the implant could accommodate 3, 6, 12
24 month or longer doses.

25

26 **Leuprolide/Tibolone**

27

28 Currently, daily doses for leuprolide are 125mcg
29 (intramuscular), and tibolone 2.5 mg (oral). Using
30 vaginal delivery analogy of 10% drug required
31 compared to oral doses daily myometrial doses could
32 be 62.5 mcg for leuprolide (50% of intramuscular

1 dose) and 250 mcg for tibolone. However in the
2 absence of clinical data, it is impossible to
3 estimate the clinical effectiveness of such doses of
4 leuprolide.

5

6 Assuming 50% w/w of drug to hydrogel, the total
7 weight of the drug/carrier layer would be in the
8 range of around 55 mg to 225 mg.

9

10 The body of the implant could accommodate 3, 6 or 12
11 month or longer doses.

12

13 **Leuprolide/Piroxicam**

14

15 Currently, daily doses for leuprolide are 125mcg
16 (intramuscular), and piroxicam 10-40 mg (oral).
17 Using vaginal delivery analogy of 10% drug required
18 compared to oral doses daily myometrial doses could
19 be 62.5 mcg for leuprolide and 3 mg for piroxicam.

20

21 A more feasible daily dose to enable drug delivery
22 via a hydrogel could be 62.5 mcg for leuprolide (50%
23 of intramuscular dose) and 300 mcg for piroxicam (1%
24 of oral dose). However in the absence of clinical
25 data, it is impossible to estimate the clinical
26 effectiveness of such doses of piroxicam and
27 leuprolide.

28

29 Assuming 50% w/w of drug to hydrogel, the total
30 weight of the drug/carrier layer would be in the
31 range of around 65 mg to 261 mg respectively.

32

1 The body of the implant could accommodate 3, 6 or 12
2 month or longer doses.

3

4 **Bacterial Vaginosis**

5

6 Bacterial vaginosis, an abnormal colonisation of the
7 vagina which may lead to vaginitis, is an
8 inflammation which occurs in the vagina. It
9 includes several strains of organism that cause
10 bacterial vaginosis, yeast infections and
11 trichomoniasis. Bacterial vaginosis occurs mostly
12 during the reproductive years although women of all
13 ages are susceptible. Typically infection affects
14 the vagina, urethra, bladder and skin in the genital
15 area.

16

17 Primary causes of bacterial vaginosis include an
18 overgrowth of anaerobic bacteria and the Gardnerella
19 organism. Although the healthy vagina includes a
20 small amount of these bacteria and organisms, when
21 the vaginal balance is disrupted by the overgrowth
22 of these bacteria, another protective aerobic
23 bacterium (lactobacilli) is unable to adequately
24 perform its normal function. Lactobacilli normally
25 provides a natural disinfectant (similar to hydrogen
26 peroxide) which helps maintain the healthy and
27 normal balance of microorganisms in the vagina. The
28 vaginal anerobic to aerobic bacteria ratio is 1000
29 to 1, normal vaginal flora is 5 to 1 ratio. During
30 vaginosis a change in pH of vaginal fluid also
31 occurs.

32

1 Bacterial Vaginosis can cause a range of symptoms
2 such as discharge. In addition, the change in pH of
3 the vaginal fluid to more than 4.5 can also cause
4 odour and some itching.

5
6 The medicament delivery device of the present
7 invention may be used to deliver medicaments to
8 restore normal vaginal bacteria by inhibiting
9 anaerobic bacteria, but not the normal vaginal
10 lactobacilli, in order to eliminate symptoms of
11 discharge and odour.

12
13 In particular embodiments, one of which is
14 illustrated in figure 2 and discussed above, the
15 medicament delivery device has a body portion for
16 insertion into the myometrium and a head portion
17 which extends into the vaginal cavity. The body
18 portion is preferably around 5 mm to 20 mm in length
19 and the head portion is around 10 to 12 mm in width.

20
21 In this embodiment the medicament is contained or
22 absorbed by or coated onto the head portion of the
23 device such that it can be released over time into
24 the vaginal cavity. Any suitable pharmaceutical
25 means may be used to carry the drug and enable its
26 release over time to the vaginal cavity.

27
28 Drugs which may be used to treat bacterial vaginosis
29 include Flagyl (also known as Metronidazole),
30 acidifiers to decrease pH to less than 5, less than
31 4.5, prebiotics, and probiotics. Other treatments
32 include cleocin, ampicillin, ceftriaxone and

1 tetracycline. Other drugs suitable for treating
2 bacterial vaginosis such as pH regulators, suitable
3 antibiotics and other drugs will be known to those
4 skilled in the art.

5
6 The location of the implant in the smooth muscle
7 myometrium of the cervix and / or part of the body
8 of the smooth muscle myometrium of the uterus allows
9 the implant to be easily inserted. During retention
10 of the implant in the myometrium of the cervix,
11 straightforward examination of the vaginal cavity 34
12 by a medical practitioner can verify that the
13 implant is in its intended position in the
14 myometrium. Whilst there is little chance of the
15 implant becoming displaced, as the retrieval means,
16 for example the cord or hook and in particular
17 embodiments the head portion remains outside the
18 myometrium, any such displacement can be easily
19 observed.

20
21 Various improvements and modifications may be made
22 without departing from the scope of the present
23 invention. For example, as detailed above the body
24 of the implant may be formed from absorbable
25 polymers. This would avoid the need to remove the
26 implant at a later date. Any suitable retrieval
27 means can be provided on the implant to allow the
28 implant to be moved into and out of the tissue of
29 the myometrium or prostate.

1 Claims

2

3 1. An implantable medicament delivery device which
4 is insertable into the female uterine myometrium or
5 the male prostate gland comprising means capable of
6 providing controlled delivery of a medicament over a
7 period of time.

8

9 2. An implantable medicament delivery device as
10 claimed in claim 1 comprising

11

12 a body having an outer surface and opposing
13 ends wherein a first end of the body has a
14 semi-sharp point.

15

16 3. An implant as claimed in claim 1 or 2 wherein
17 the implant is absorbable.

18

19 4. A device as claimed in claim 2 or 3 wherein the
20 body is elongate and at the second end includes a
21 head portion wherein the head portion is a lateral
22 extension from the longitudinal axis of the elongate
23 body.

24

25 5. The device of claim 4 wherein the head portion
26 is a substantially flat plate which extends in all
27 radial directions from the second end of the body of
28 the device.

29

30 6. A device as claimed in claim 4 or 5 wherein, in
31 use, the head portion allows manipulation and
32 surveillance of the implant.

1 7. The device of any preceding claim wherein the
2 means capable of providing controlled delivery of a
3 medicament are provided in or on the body of the
4 implant.

5

6 8. The device of any of claims 4 to 7 wherein the
7 means capable of providing controlled delivery of a
8 medicament are provided in or on the head portion of
9 the implant.

10

11 9. The device of any of claims 2 to 8 wherein the
12 second end comprises retrieval means.

13

14 10. The device of any preceding claim wherein the
15 device retrieval means is an elongate flexible
16 member.

17

18 11. The device according to any preceding claim
19 which has an axial length from 5 mm to 45 mm.

20

21 12. The device according to any preceding claim
22 which has a diameter of from 0.5 mm to 4 mm.

23

24 13. A device according to any preceding claim
25 comprising at least one medicament.

26

27 14. The device as claimed in claim 13 wherein the
28 least one medicament is selected from anti-
29 infectives, antimicrobials, prebiotics, probiotics,
30 acidifiers, antivirals, antibiotics, anti-
31 allergens, anti-inflammatories, anti-fungals,
32 anti-cholinesterases, nutritional agents,

1 cardiovascular agents, anti-hypertensive agents and
2 chemotherapeutic agents.

3

4 15. The device as claimed in claim 13 or 14 wherein
5 the device comprises a medicament for oestrogen
6 dependent proliferative disorders of the pelvis for
7 example endometriosis or fibroids.

8

9 16. The device according to any one of claims 13 to
10 15 wherein said the medicament is at least one
11 member chosen from the group including progestins,
12 GnRH agonists / antagonists, NSAIDs, COX-II
13 inhibitors, combined oral contraceptives, Danazol,
14 smooth muscle relaxants or aromatase inhibitors.

15

16 17. The device according to any preceding claim
17 wherein, in use, the cumulative release of
18 medicament is in an amount selected from 5%, 10%,
19 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%,
20 95% or 99% relative to the total amount of
21 medicament in the device after implantation for a
22 period of 1 day, 1 week, 2 weeks, 1 month, 2 months,
23 3 months, 4 months, 6 months, 1 year, 2 years, 3
24 years, 4 years or 5 years.

25

26 18. A kit for implanting a device as claimed in any
27 of claims 1 to 17 comprising

28 a device as claimed in any of claims 1 to 15;

29 and

30 an insertion tool comprising an elongate shaft,
31 said shaft having a handle means at a first end
32 thereof and device mounting means at a second

1 opposite end wherein the medicament delivery
2 device is mountable on the device mounting
3 means of the insertion tool.

4

5 19. A method for introducing a medicament into the
6 body of a female mammal, comprising the step of
7 inserting a device according to claims 1 to 17 into
8 the myometrium.

9

10 20. A method as claimed in claim 19 comprising the
11 steps of

- 12 - providing the implantable medicament
- 13 delivery device of claims 1 to 15;
- 14 - introducing the medicament delivery device
- 15 into the body via the vagina;
- 16 - penetrating the myometrium; and
- 17 - inserting the medicament delivery device
- 18 into the myometrium.

19

20 21. The method as claimed in claim 20 wherein the
21 medicament implantable device is introduced into the
22 body using an insertion tool.

23

24 22. Use of an implantable medicament delivery
25 device as claimed in claims 1 to 17 to provide long
26 term local delivery of medicaments to the vaginal
27 cavity and epithelium and thereby into the pelvic
28 region and organs thereof including to the bladder,
29 peritoneum, vulva, vagina, ovaries, fallopian tubes
30 and/or the uterus and/or then into the bloodstream.

31

- 1 23. Use of an implantable medicament delivery
2 device as claimed in claims 1 to 17 to provide long
3 term local delivery of medicaments to the myometrium
4 and thereby into the pelvic region and organs
5 thereof including to the bladder, peritoneum, vulva,
6 vagina, ovaries, fallopian tubes and/or the uterus
7 and/or then into the bloodstream.
- 8
9 24. Use of an implantable delivery device as
10 claimed in claims 1 to 17 to provide long term local
11 delivery of medicaments to the prostate gland,
12 seminal vesicles, rectum, bladder and/or tissues
13 and/or pelvic region and/or organs thereof and/or
14 then into the bloodstream.

1/14

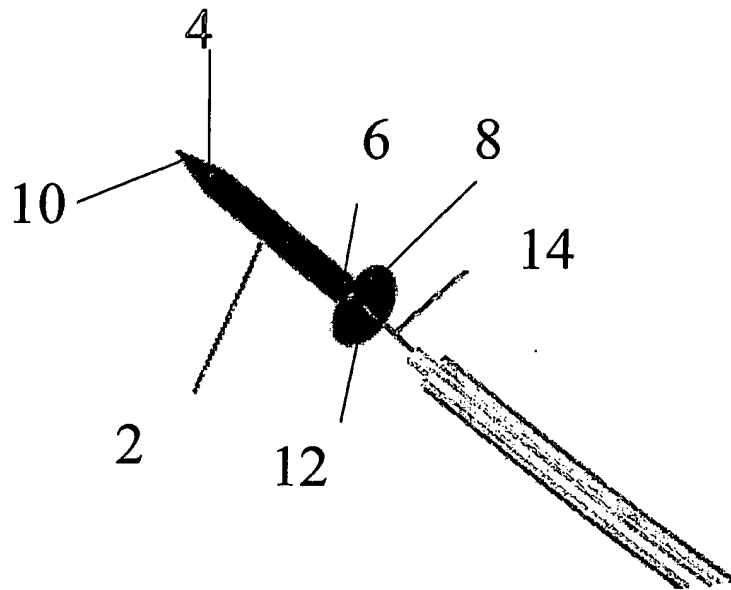


Figure 1

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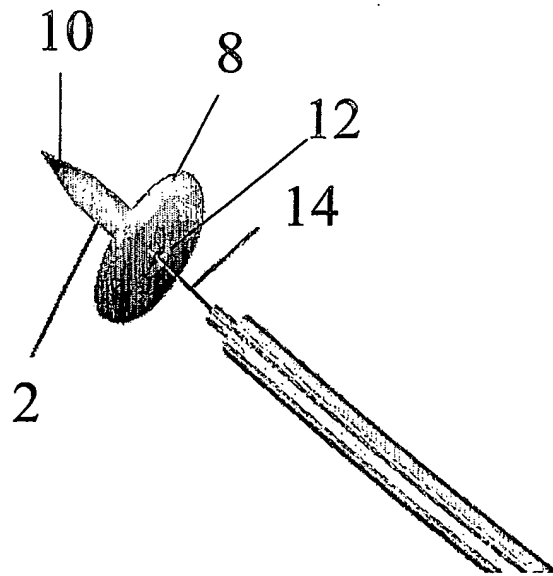


Figure 2

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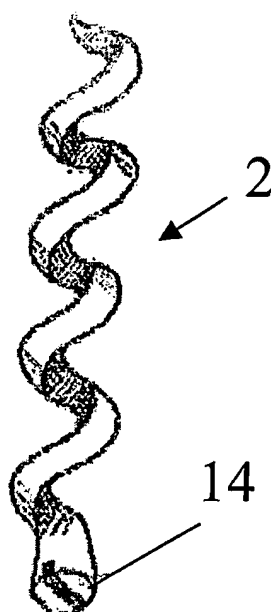


Figure 3

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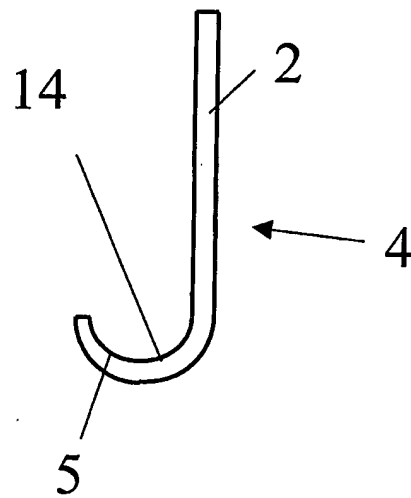


Figure 4

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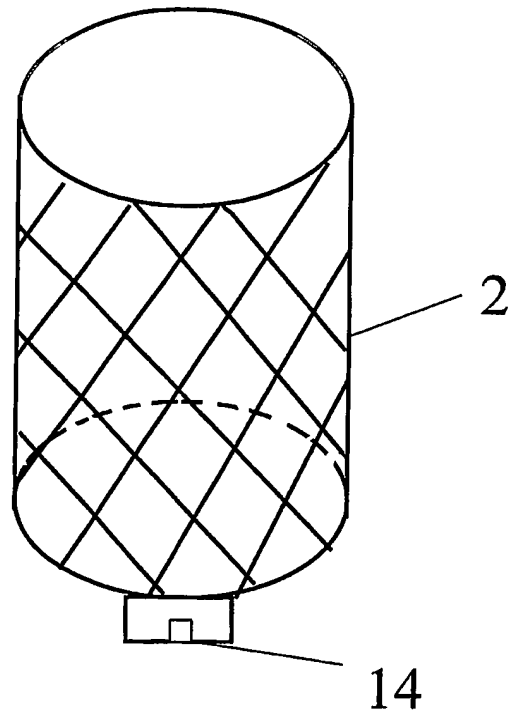


Figure 5

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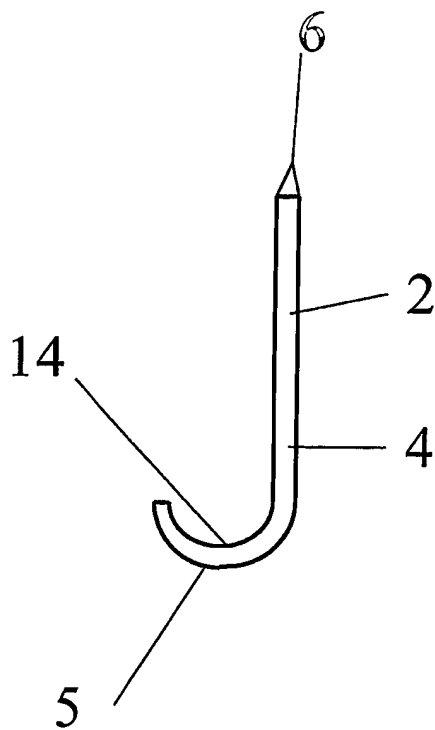


Figure 6

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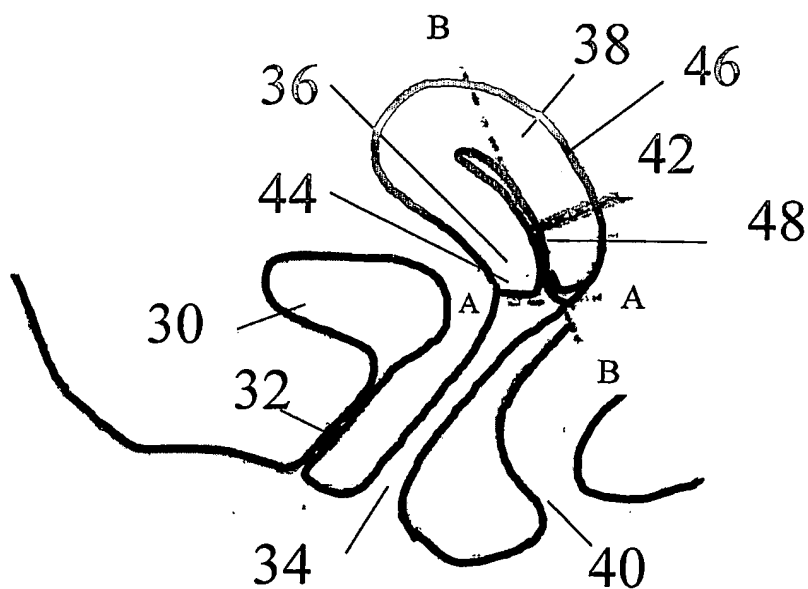


Figure 7

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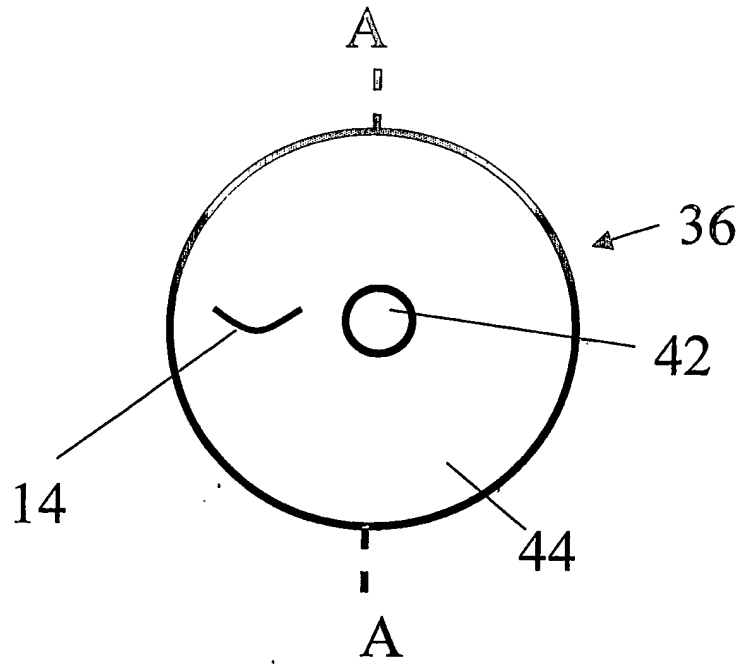


Figure 8

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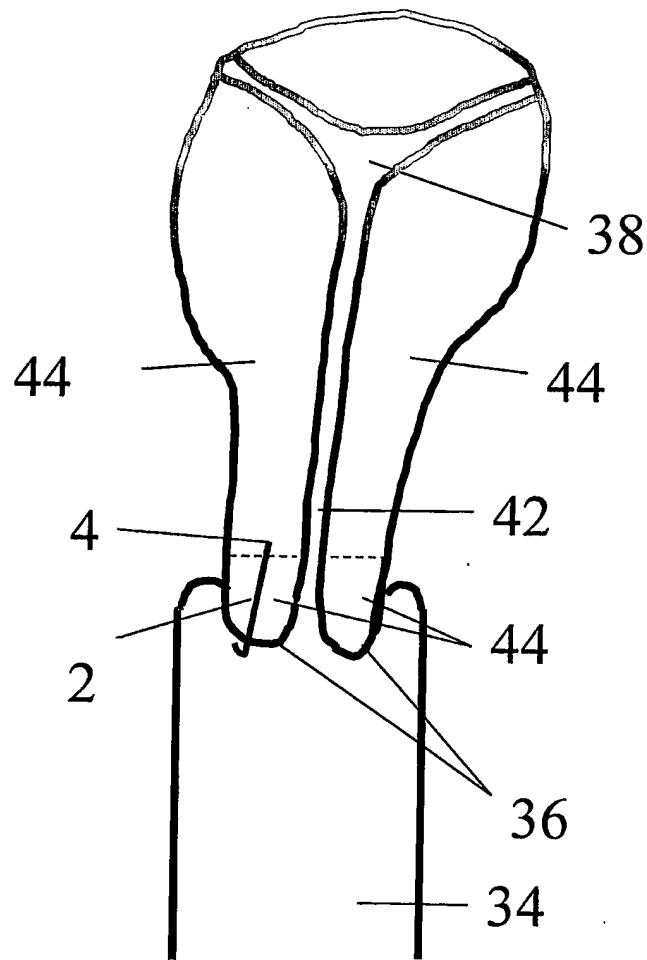


Figure 9

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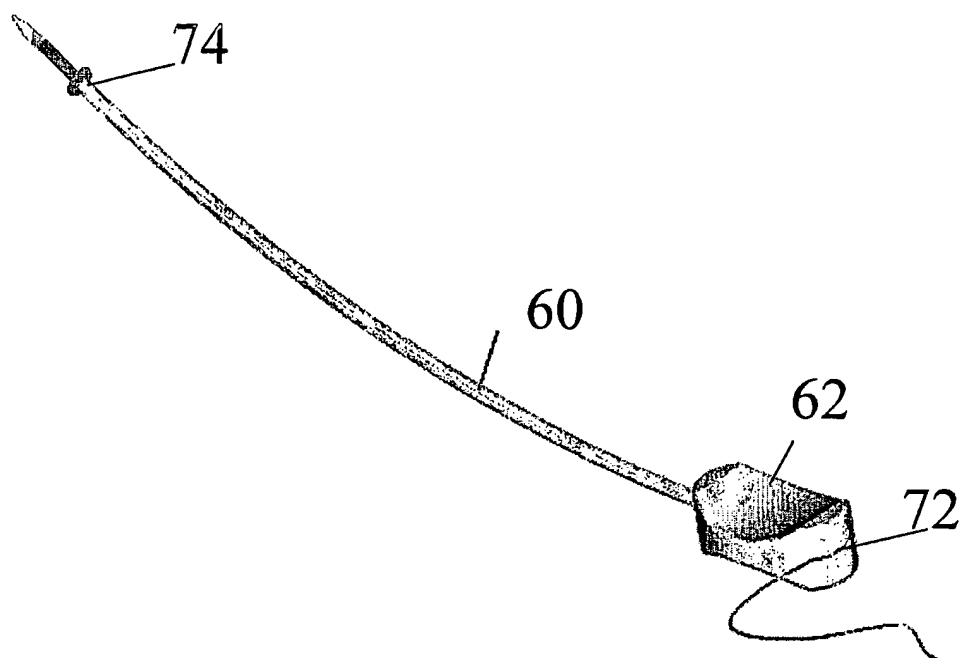


Figure 10

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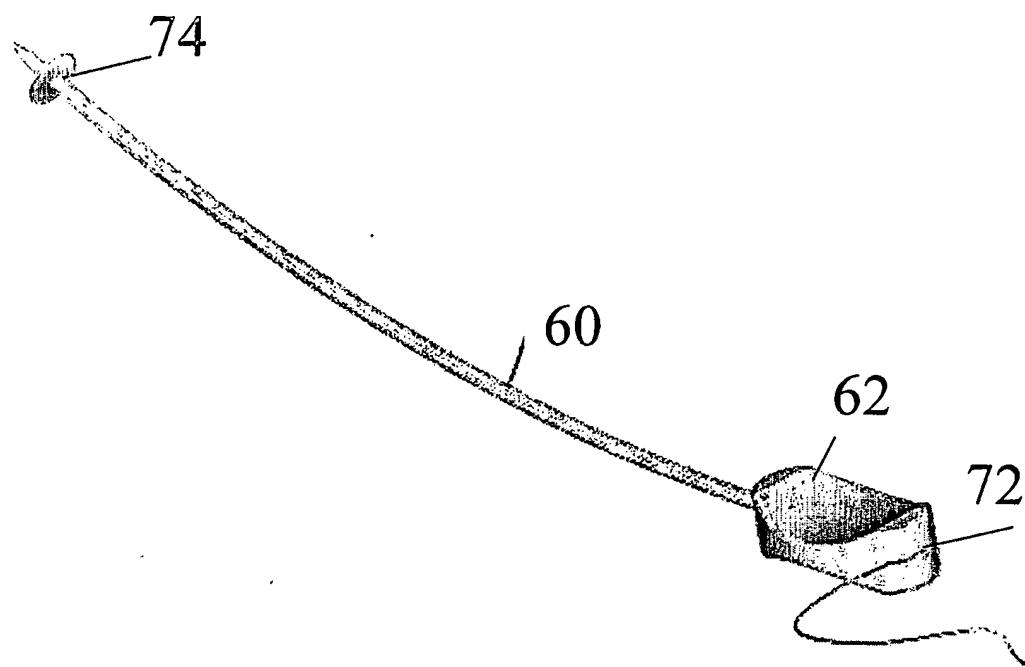


Figure 11

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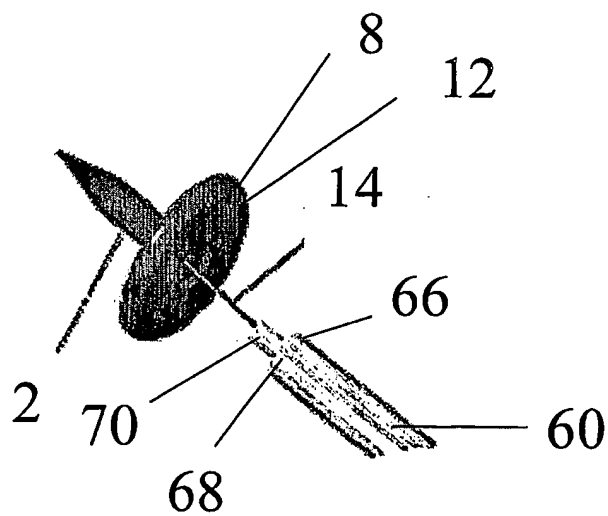


Figure 12

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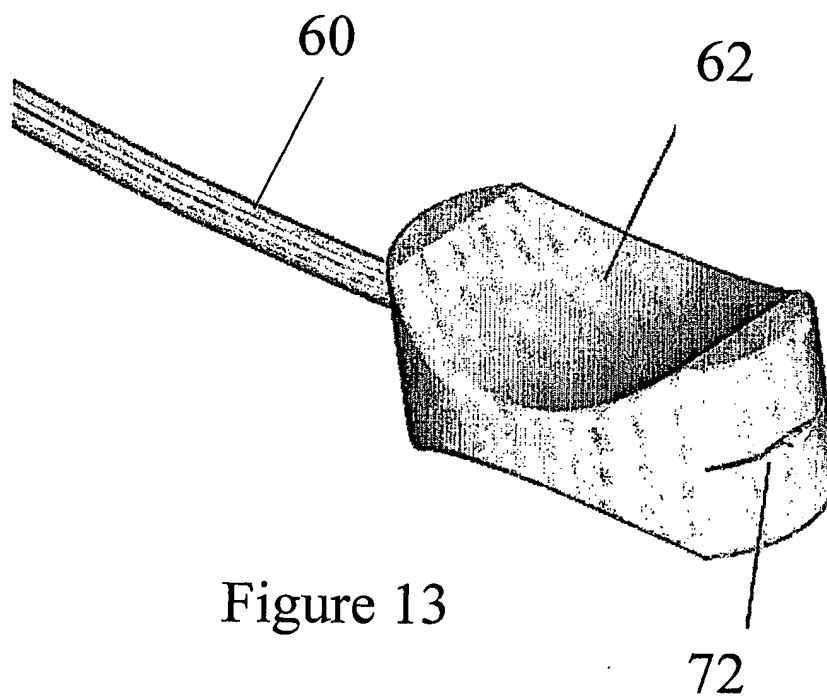


Figure 13

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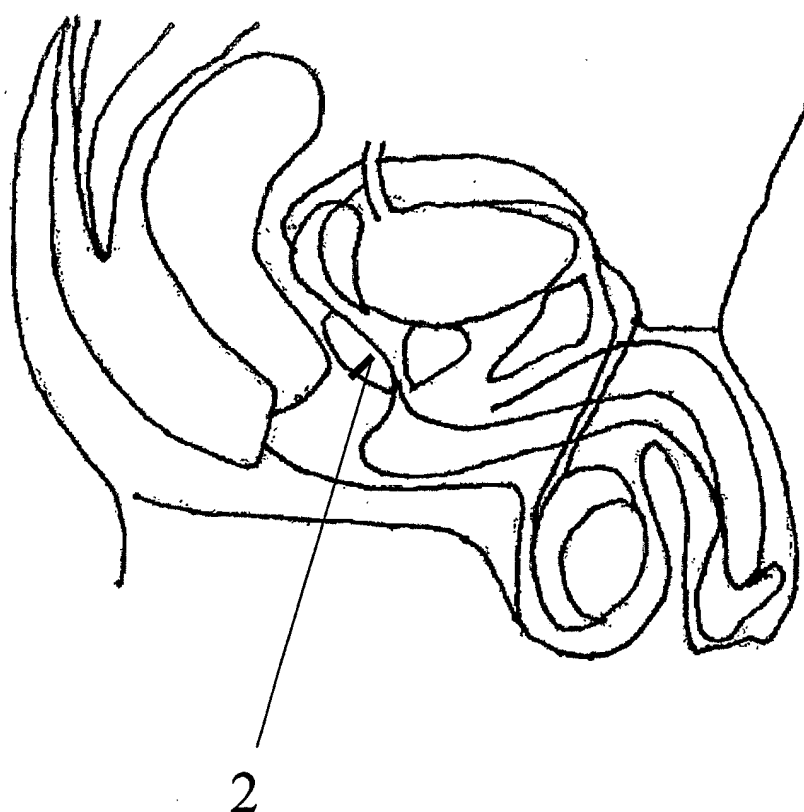


Figure 14

INTERNATIONAL SEARCH REPORT

national Application No
T/GB2004/001390

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61F2/02 A61F6/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

17 August 2004

Date of mailing of the international search report

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/001390

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the medicament.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

national Application No
T/GB2004/001390

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